REMARKS

Claims 1 and 6-20 are pending in the instant application. Claims 1 and 6-20 have been rejected. Claims 1, 12-14 and 20 have been amended. A replacement Sequence Listing is provided herewith. No new matter has been added by these amendments. Reconsideration is respectfully requested in light of these amendments and the following remarks.

I. Rejection of Claims Under 35 U.S.C. 112, First Paragraph

Claims 1 and 6-20 have been rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. The Examiner suggests that the claims identify the c-raf gene in name only and as such applies to all c-raf sequences yet the specification as filed fails to provide written support for the broad genus. Applicant has amended claims 1, 12-14 and 20, and their dependent claims, to recite that the raf gene is human c-raf (SEQ ID NO: 64). Support for this amendment to the claims can be found at pages 22-42. Claims 12-14 and 20 have

been made independent claims, incorporating the limitations of claim 1, in order to more clearly define the instant invention. No new matter has been added to these claims. Accordingly, the claims as amended meet the requirements of 35 U.S.C. 112, first paragraph. Withdrawal of this rejection is therefore respectfully requested.

II. Rejection of Claims Under 35 U.S.C. 102(b)

Claims 1 and 12 have been rejected under 35 U.S.C. 102(b) as being anticipated by Carroll et al. (1991). The Examiner suggests that this reference discloses an 18 mer oligonucleotide that hybridizes with and inhibits expression of c-raf. Applicant respectfully traverses this rejection.

As discussed *supra*, Applicant has amended claim 1, and by dependency claim 12, to recite that the antisense compounds of the instant invention are targeted to human c-raf of SEQ ID NO: 64. The reference of Carroll et al. (1991) discloses only a single antisense compound targeted to codons 1-6 of murine, not human, c-raf. No other antisense compounds are taught or suggested by this reference. In order to anticipate a claim the cited reference must teach each and every limitation of the claim

(MPEP 2131). This reference fails to teach antisense compounds to human c-raf of SEQ ID NO: 64 and thus cannot anticipate the claims as amended. Withdrawal of this rejection is respectfully requested.

III. Rejection of Claims Under 35 U.S.C. 103(a)

Claims 1 and 6-11 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Carroll et al. (1991) in view of Cook (WO 93/13121) and Skorski et al. (1993). The Examiner suggests that it would have been *prima facie* obvious for one of ordinary skill to incorporate the modifications of Cook et al. and the chemotherapeutic compounds of Skorski et al. into the antisense of Carroll et al. The Examiner suggest one of skill would have been motivated because Skorski et al. teaches that such combinations have additive effects in treating cancer while Cook et al. teach the utility of modified antisense oligonucleotides. The Examiner suggests that a reasonable expectation of success is provided by the teachings of Cook et al. and Skorski et al. who teach the steps and provide examples of how to make such compounds, which is also routine in the art. Applicant respectfully traverses this rejection.

As discussed *supra*, the primary reference of Carroll et al. fails to teach the antisense compounds as recited in the amended claims which are targeted to human c-raf of SEQ ID NO: 64. Nowhere does this reference teach or suggest making such antisense compounds as now claimed, nor does it provide any motivation or expectation of success for such antisense compounds.

The secondary references cited, even when combined with this reference, fail to overcome the deficiencies in teaching of this primary reference.

Cook et al. (WO 93/13121) disclose only modified oligonucleotides to elicit RNase H for strand cleavage. Nowhere does this patent application teach or suggest antisense compounds as claimed which are targeted to human c-raf (SEQ ID NO: 64) or the successful use of such compounds to inhibit c-raf expression.

Skorski et al. (1993) disclose the combination of chemotherapeutic agents, specifically mafosamide, with antisense to bcr-abl transcripts to inhibit proliferation of Philadelphia leukemic cells. Nowhere does this paper teach or suggest antisense compounds as claimed which are targeted to human c-raf

(SEQ ID NO: 64) or the successful use of such compounds to inhibit c-raf expression.

To establish a *prima facie* case of obviousness, three basic criteria must be met. MPEP 2143. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art must teach or suggest all claim limitations. The limitations of the claims as now amended, which specify antisense to human c-raf (SEQ ID NO: 64), are not taught or suggested by any of the references individually or when combined. Therefore, the limitations of the claims as amended clearly are not taught or suggested by the combination of prior art references, nor is any expectation of successful use of such antisense compounds provided by the combination of prior art. It is only with the specification in hand that one of skill would understand that specific regions of this gene could be targeted successfully with antisense compounds. Thus, the combination of prior art cited cannot render the instant claimed invention

obvious. Withdrawal of this rejection is therefore respectfully requested.

IV. Replacement Sequence Listing

Applicants have identified inconsistencies between the Specification and Sequence Listing. To rectify these inconsistencies, Applicants have now identified the sequences found in the Sequence Listing in the order presented in the specification. Amendments to the Sequence Listing are summarized in the following Table.

Original Sequence Listing	Amended Sequence Listing to Correspond with the Specification
SEQ ID NO:1-24	SEQ ID NO:1-24
SEQ ID NO:25	SEQ ID NO:64
SEQ ID NO:26-28	SEQ ID NO:25-27
SEQ ID NO:29	SEQ ID NO:65
SEQ ID NO:30-65	SEQ ID NO:28-63
SEQ ID NO:66-70	DELETED

SEQ ID NO:71	SEQ ID NO:66
SEQ ID NO:72-88	DELETED
SEQ ID NO:89	SEQ ID NO:67
SEQ ID NO:90-130	SEQ ID NO:68-108

V. Conclusion

Applicant believes that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,

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